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(71) Applicant: BRISTOL-MYERS SQUIBB COMPANY [US/US]; Route 206 and Provinceline Road, P.O. Box 4000, Princeton, NJ 08543-4000 (US).

(72) Inventor: RAYBURN, James, W.; 1601 N. Red Bank Road, Evansville, IN 47720 (US).

(74) Agent: RYAN, Richard, P.; Bristol-Myers Squibb Company, 5 Research Parkway, Wallingford, CT 06492 (US).

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(54) Title: NOVEL PHARMACEUTICAL SALT FORM

(57) Abstract

The saccharinate salt of synthetic non-alkaloidal medicinal organic bases provides a novel salt form possessing improved organoleptic properties as well as reduced solubility.

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NOVEL PHARMACEUTICAL SALT FORM

Cross Reference to Related Application

This application claims priority from provisional application USSN 60/098,154 filed August 27, 1998.

Background of the Invention

The present invention relates to a novel salt form of certain pharmacologically active organic bases and their preparation. The class will be exemplified by the saccharinate salt of buspirone, a useful anti-anxiety agent.

It is known that while many organic bases function as useful pharmacologic agents, nonetheless salt forms are often pharmaceutically preferred for reasons of enhanced solubility, ease of compounding, and stability. It is also well accepted that oral dosing of drugs is a preferred route of administration. However, most organic bases possess a very bitter taste which, for acceptable oral administration, requires masking by various methods familiar to pharmaceutical formulation practitioners such as the incorporation of sweeteners, flavorings, organoleptic enhancers, and the like.

The intense bitter taste of most bases can be relieved somewhat by substituting a salt form of the pharmacologically active agent for the base in pharmaceutical formulations; e.g., the hydrochloride salt. Some salt forms of drugs are more effective than others in reducing the objectionable taste of the pharmaceutical formulation. It is known that patient compliance in adhering to a drug regimen is negatively affected by pharmaceutical products that are objectionable in taste, particularly in instances where the patient disorder is accompanied by loss of appetite, nausea, and vomiting.

In U.S. 4,362,730, Räder, et al. disclosed and claimed the saccharinate salt of vincamine, a pharmaceutically active alkaloid. Vincamine saccharinate was described as having improved solubility and taste characteristics. Greater solubility for the saccharinate salt of vincamine differs from the reduced solubility seen for the saccharinates of the present convention.

The present invention concerns a novel salt form of non-alkaloidal medicinal organic bases that renders the normally bitter-tasting drug much more palatable, thereby facilitating its pharmaceutical formulation for oral routes of administration where taste comes into play; such as liquid suspensions, lozenges, chewable tablets, chewing gums, and the like. When applied to synthetic organic base medicinals, as opposed to alkaloids, solubility of the salt is generally less than for more standard pharmaceutical salts such as halides, sulfates, and the like.

Detailed Description of the Invention

The saccharinate salt of certain non-al\kaloidal organic bases provides novel salt forms demonstrating improved organoleptic properties. For certain medicinals the saccharinate salt also provides a means of sustaining drug release by virtue of decreased aqueous solubility of the saccharinate compared to more standard pharmaceutical salts such as halides, sulfates, phosphates, and the like. The saccharinate salts are conveniently synthesized by salt interchange on admixture of solutions of sodium saccharinate and acid addition salts; e.g., the hydrochloride salt, of medicinal organic bases. Other salt-forming reactions, well-known to one skilled in the pharmaceutical sciences, may also be employed.

Various classes of orally-active non-alkaloidal synthetic medicinal organic bases are intended applications of the present invention. Some of these medicinal bases fall into the following medical use categories:

- antiinfectives such as erythromycin;
- oncolytics;
- analgesics such as codeine, meperidine, pentazocine, butorphanol, buprenorphine;
- psychopharmacologics;
- neurologics;
- anesthetics;

- respiratory agents;
- cardiovasculars/cardio-renal agents
- endocrine agents;
- metabolic agents;
- gastrointestinal agents;
- antiallergenics; and
- immunologics.

Psychopharmalogics can be subclassed as:

- anxiolytics; e.g., benzodiazepines such as alprazolam, azapirones such as buspirone;
- antipsychotics; e.g., phenothiazines such as chlorpramazine and thioridazine, piperazines such as fluphenazine, thioxanthenes such as thiothixene, butyrophenones such as haloperidol, dibenzoxapines such as loxapine, dihydroindolones such as molindone; and
- affective disorder agents such as imipramine, trazodone, nefazodone, fluoxetine, sertraline, and the like, dextroamphetamine and methylphenidate.

Neurologics can be represented by procyclidine, biperiden, amantadine and selegiline; ergotamines and methylsergide; scopolamine, cyclizine, hydroxyzine and the like.

Anesthetics are represented by benzocaine, dibucaine, lidocaine, procaine and the like.

Respiratory agents are represented by epinephrine, phenylephrine, phenylpropanolamine and pseudoephedrine; isoproterenol and terbutaline.

Cardiovasculars can be subclassed as:

- inotropics such as dobutamine;
- antiarrhythmics such as acecainide, disopipramide;
- β-blockers such as propranolol, atenolol, nadolol;
- calcium blockers such as diltiazem, nifedipine and nimodipine;
- vasodilators such as papaverine and isoxsuprine;
- antihypertensives such as hydralazine; and
- diuretics such as triamterene and amiloride.

Endocrine agents such as bromocryptine and clomiphene; and metabolic agents such as phenformin.

Gastrointestinal agents such as metaclopramide or cimetidine.

The present invention involves stable crystalline saccharinate salts of orally administrable medicinal bases. Saccharin, chemically 1,2-benzisothiazol-3(2H)-one 1,1,dioxide, is used as a sweetener, most commonly in the form of its sodium salt dihydrate. While it is used as a sweetener in pharmaceutical applications, its use is as a component of a mixture of ingredients. While saccharine provides a sweet taste in dilute aqueous solutions where it is about 500 times sweeter than sugar with the sweet taste still detectable in 1:100,000 dilution; nonetheless saccharin has a bitter, metallic aftertaste. Because saccharin's taste is most pleasant in dilute solution, care must be exercised in formulating saccharin in its solid state because of a very objectionable taste.

By contrast the current invention relates to actual salt forms, as opposed to mixtures, comprising the organic base cation and the

saccharinate anion. In this form the medicinal has pleasant organoleptic properties even in its solid form. As such, the saccharinate salts offer the potential for pharmaceutical formulations without requiring large amounts of other organoleptic enhancers such as sweeteners, flavors, and the like which are usually required to render medicinal bases palatable. The advantages of saccharinate salts would especially be evident in formulating oral suspensions, chewable tablets, lozenges, and quick-melt dosage forms.

Another aspect of the present invention relates to the general reduction in solubility of the saccharinate salts of the non-alkaloidal medicinal bases compared to more common acid addition salts of the medicinal bases such as hydrohalide, sulfate, phosphate salts and the like. With reduced solubility drug release is slowed and extended release of the drug usually occurs. Therefore, the saccharinate salts offer a method for providing extended release dosing for certain medicinals.

The present invention is illustrated by the following examples but is not limited to them.

Example 1 - Buspirone Saccharinate

Buspirone hydrochloride (8-4[4-(2-pyrimidinyl)-1-piperazinyl])butyl]-8-azaspiro[4.5]decane-7,9-dione hydrochloride 4.22 g, 10 mmole) dissolved in a minimal amount of water was added to a concentrated solution of sodium saccharinate (2.05 g, 10 mmole) with stirring. The mixture was chilled and the supernatant aqueous layer decanted from the heavier oil layer which was dissolved in methylene chloride. The methylene chloride solution was washed with water and then dried ($MgSO_4$). The dried solution was filtered and concentrated in vacuo to a clear oil. Trituration in ether provided a pale yellow saccharinate salt, m.p. 142-145 °C.

Analysis:

Calculated for $C_{21}H_{31}N_5O_2 \bullet C_7H_5NO_3S$: C, 59.14; H, 6.38; N, 14.78; S, 5.64.

Found: C, 59.14; H, 6.46; N, 14.89; S, 5.51.

Example 2 - Taste Preference Testing

Under single-blind conditions, three small glass plates were set out for taste-testing. Plate #1 contained buspirone hydrochloride. Plate #2 contained buspirone saccharinate, and Plate #3 contained 1:1 molar equivalent amounts of buspirone hydrochloride and sodium saccharinate in the form of a physical mixture. Tasting volunteers were asked to taste each of the samples and give their preference. All volunteers selected Plate #2 (buspirone saccharinate) as the best tasting sample. By contrast, both Plates #1 and #3 were labeled as objectionable to highly objectionable in taste by the volunteers.

Claims

1. The saccharinate salt of non-alkaloidal organic medicinal bases capable of acid addition salt formation.

2. The salt of claim 1 wherein the base is a useful non-alkaloidal orally-active drug selected from the group consisting of psychopharmacologics, analgesics, neurologics, anesthetics, respiratory agents, cardiovascular-renal agents, hematologic agents, endocrine and metabolic agents, gastrointestinal agents, dermatologic agents, antiinflammatories, antiallergics, immunologics, oncolytics, and antiinfectives.

3. The salt of claim 2 wherein the base is a useful orally-active antiinfective agent.

4. The salt of claim 2 wherein the base is a useful orally-active analgesic agent.

5. The salt of claim 2 wherein the base is a useful orally-active cardiovascular-renal agent.

6. The salt of claim 2 wherein the base is a useful orally-active gastrointestinal agent.

7. The salt of claim 2 wherein the base is a useful orally-active neurologic agent.

8. The salt of claim 2 wherein the base is a useful orally-active psychopharmacologic agent.

9. The psychopharmacologic agent of claim 8 that is useful in depression.

10. The psychopharmacologic agent of claim 8 that is useful in anxiety.

11. The psychopharmacologic agent of claim 10 that is an azapirone.

12. The azapirone of claim 11 selected from buspirone and gepirone.

13. The azapirone of claim 11 is buspirone saccharinate.

14. The method of producing a saccharinate salt comprising the mixing of a solution of an acid addition salt of the medicinal base with a solution of sodium saccharinate.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/19575

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :A61K 9/16, 9/22, 9/58

US CL :424/441, 497; 514/951

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/441, 497; 514/951

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

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C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	FR 1,288,002 A (SYNERHOLM et. al.) 12 February 1962, Table at the bottom of page 2	1, 2, 5, 14 --- 3, 4, 6-13
Y, P	US 5,837,277 A (HAYWARD) 17 November 1998, col. 3, line 64.	1-14

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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